REMARKS

Claims 1, 3-6, 8 and 9 are pending in the application and stand rejected. Reconsideration and withdrawal of the rejections is requested in view of the following remarks.

Rejection under 35 U.S.C §103

Claims 1, 3-6, 8 and 9 stand rejected under 35 U.S.C. 103(a) as being obvious over U.S. Pat. No. 4,849,141 ("'141 patent") to Fujioka et al. in view of the article "Collagen-biomaterial for drug delivery" by Friess ("Friess"). The Office Action states that the '141 patent discloses a method for preparing a formulation comprising collagen, solvent and glucose wherein the formulation is cross-linked using UV irradiation or γ irradiation. The Office Action further states that the Friess is relied upon solely for the teaching that γ -irradiation is known effective method for sterilizing collagen.

Applicant has amended claims 1 and 6 to specify that the composition comprises collagen and a sugar material that has been irradiated with ultraviolet radiation so as to form glucose-derived crosslinked collagen.

The '141 patent teaches a method for preparing a molding material for use in making sustained released formulation. The '141 patent specifically teaches and emphasizes throughout its specification that such a formulation "must be uniform" and "homogenous" and that where the "molding material consists of collagen...the molding material cannot exist in the form of a uniform and homogenous solution." [See '141 patent at column 1, lines 32-41]. As such, the '141 patent is particularly concerned with reducing the "fiber-forming property" of collagen. [See '141 patent at column 1, lines 25-44]. To this end, the '141 patent teaches a method of preparing a "uniform and high

concentrated mixture" of collagen "without causing fiber-formation" by use of low pH and specific salt concentrations. [See '141 patent at column 2, lines 20 – 29]. Although the '141 patent discloses the use of glucose, the glucose is added "because the solubility of collagen and/or gelatin is increased by such addition" [see '141 patent at column 2, lines 51-54]; or "where it is impossible to lower the salt concentration." [See '141 patent at column 5, lines 8 – 13].

In contrast, the present invention teaches a composition having collagen and sugar material which has been exposed to UV radiation, where such treatment results in formation of glucose-derived cross-linked collagen. In the present invention, the incorporation of glucose into collagen synergistically enhances UV-induced cross linking to yield a material with greater durability. The '141 patent does not teach the use of UV radiation of a composition comprising collagen and a glucose material so as to form glucose-induced crosslinked collagen as is taught by the present invention. Instead, the '141 patent teaches UV irradiation or γ irradiation as an optional additional processing step for controlling the release rate of the active ingredient. As the '141 patent specifically teaches:

> [a]dditional processings can be effected on the final product obtained above for the purpose of further controlling the release rate of the active ingredient. Such processings include the formation of crosslinking, with the crosslinking agent, UV irradiation or γ irradiation among the collagen and/or gelatin contained in the product, or where appropriate, between the collagen and/or gelatin and the active ingredient. The crosslinkage may be of a covalent bond or an ionic bond. The crosslinkage can be effected, for instance, by immersing the product in a suitable crosslinking agent such as an aqueous aldehyde solution (e.g. formaldehyde, acetaldehyde or glutaraldehyde), or an alcohol solution containing a diisocyanate (e.g. hexamethylene diisocyanate), or by

> contacting the product with a gaseous crosslinking agent selected from the above.

'141 patent, column 6, lines 45 – 60.

Nowhere in the '141 patent is there discussion or suggestion of the use of glucose and UV or γ irradiation for the purpose of forming glucose-derived crosslinked collagen. In addition, the '141 patent does not teach or suggest that UV or gamma irradiation of a composition comprising collagen and a glucose material is useful or desirable for its ability to form glucose-derived crosslinked collagen. As stated above, the '141 patent only teaches the use of glucose as desirable for increasing the solubility of collagen for forming a uniform product. A detailed review of the entire specification of the '141 patent, reveals only the following passage relating to the use of glucose:

> (3) To add glucose to the mixture. This process is particularly advantageous where the mixture has nearly neutral pH, because the solubility of collagen and/or gelatin is increased by such addition.

'141 patent, column 2, lines 51-54.

The Office Action also states that the '141 teaches the desire to preserve and stabilize the formulation by adding preservatives and stabilizers and that because Friess teaches that γ irradiation is the method of choice to sterilize collagen biomaterials mainly for its high efficacy and accurately controlled dose, it would have been obvious to one having ordinary skill in the art to provide a formulation comprising collagen and glucose that is cross-linked by UV radiation, and instead of using stabilizers or preservatives as disclosed by the '141 patent, the skilled artisan would γ irradiate the formulation as disclosed by Friess.

Applicant wishes to point out that Friess is a review article which attempts to briefly summarize the art relating to Collagen. [See, title of Friess, "Review article

Collagen-biomaterial for drug delivery"], and that while a particular sterilization technique may be highly effective, it may not necessarily be desirable nor applicable for particular end-uses. In other words, efficacy does not equate to desirability.

Friess' comment that γ irradiation is "a method of choice to sterilize collagen biomaterials mainly for its high efficacy and accurately controlled dose" is further reviewed in light of the references cited by Friess. A reading of Friess' cited references provides better context of the state of the art and expands on this statement. For example, where Friess acknowledges that "[s]tudies on the effect of γ-irradiation on collagen structure clearly indicate chain scission resulting in a fraction of lower molecular weight material" and that "[t]hese molecular changes due to γ-sterilization reduce the mechanical strength of collagen," (page 121, paragraph 3.5.2), Friess cites Cheung et al., "The effect of γ-irradiation on collagen molecules, isolated α-chains, and crosslinked native fibers," *J. Biomed. Mat. Res.*, vol. 24, 581-589 (1990) (See Friess, paragraph 3.5.2, page 121, reference 153).

Cheung clearly states what was known to one of ordinary skill in the art at the time of filing of the present application. Specifically, that "[t]he search for an effective sterilization process that will not destroy the structural integrity of bioprosthesis, particularly those which involve biopolymers, has become a major challenge in the field of biomaterials." [See, Introduction]. In fact, the primary purpose of this reference is to report "how collagen molecules are readily damaged by γ-radiation at dosages commonly used for sterilizing biomedical products." [See, Cheung, Abstract]. Cheung concludes by stating that "[a] question which remains is whether the damage of some peptide bonds in a collagenous matrix can be compensated by the formation of

crosslinks." [See, Cheung et al., page 588, 2nd paragraph]. As such, one of ordinary skill in the art would not have γ-irradiated a collagen and glucose material composition with the reasonable expectation that the γ-irradiation would provide desirable results.

The Office Action also relies on Friess' statement that "fragmentation may be compensated by the formation of additional crosslinks," [See Friess, paragraph 3.5.2, page 121]. Here, Friess cites Damink et al. ("Daminik"), "Influence of ethylene oxide gas treatment on the in vitro degradation behavior of dermal sheep collagen," *J. Biomed. Mat. Res.*, vol. 29, 149-155 (1995) (Friess reference 150].

Damink reports on the advantages of ethylene oxide gas treatment as compared to γ-sterilization because "γ-sterilization induc[es] chain scission...result[ing] in a decreased tensile strength and...made the samples more susceptible toward degradation." [See Damink, p. 154, last sentence]. Damink also reports that γ-irradiation of cross-linked collagen still induced chain scission, resulting in a decrease of tensile strength. [See Damink, Abstract]. Damink further teaches that use of ethylene oxide gas is more favorable as it has less impact on the mechanical properties of collagen as compared to treatment with γ-irradiation. These references teach the undesirability of using γ-irradiation as a method of sterilizing collagen.

Thus, Friess, when read in the context of its supporting references, clearly teaches away from using γ-irradiation on collagen where the strength of the composition is of importance. Furthermore, there is no mention of glucose in combination with collagen anywhere in Friess, and thus no reason for the skilled person to expect that γ-irradiation on such a compound would provide desirable results.

Finally, the prior art references when combined must teach or suggest all the claim limitations." MPEP §2142. However, there is no mention or hint of the use of UV radiation of a composition comprising collagen and a glucose material so as to form glucose-induced crosslinked collagen as recited by the present independent claims. Even if the references were to be combined, the proposed combination would not reach the claimed invention, which is directed to, inter alia, the glucose-derived crosslinked collagen.

In view of the foregoing, it is submitted that the claims are in condition for allowance. Applicants respectfully request a Notice of Allowance. If anything can be done to speed the allowance of this case, Examiner is asked to telephone the undersigned.

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